REMARKS

I. Claim Amendments

New claims 226-228 recite limitations that were presented in claims that are currently withdrawn due to the species election. The new claims ultimately depend from claim 206 and therefore provide further refinement of the claimed method. These amendments do not add new matter to the application.

The Office Action Summary lists claim 214 as withdrawn. However, this claim reads on an elected species because the claim-recited "inflammatory marker" may be the elected species "leukotriene levels." Therefore, the Applicants request that this claim be considered as pending and currently be examined.

II. Information Disclosure Statement

The Applicants thank the examiner for considering various information disclosure statements that have been filed. The examiner's notation that items C81, C121-C125 and C128-C130 have not been considered because these documents lack a publication date is confusing. First, to the extent some of the documents may be available through WIPO, the documents are published. However, the documents are being submitted because they are foreign search reports that the PTO may wish to consider, not because they are published references. While the Patent Office may choose not to list the documents as "references" on the face of an eventual patent, there is no rule stating that only "publications" may be submitted by an applicant or considered by an examiner.

Genbank entries are published on the National Center Biotechnology Information Website (http://www.ncbi.nlm.nih.gov/) and have a publication date listed on the upper right hand corner of the print outs. Furthermore, examiners in art group 1600 frequently cite sequences published on Genbank for prior-art rejections and therefore it is important to consider these disclosed sequences. For the Examiner's convenience, an additional Form 1449 is provided in which the publication dates for the journal article of document C81, Genbank entries (documents C129 an d C130) and International Search Reports (documents C121-C125 and C128) are listed. Copies of the references were submitted with the previous information disclosure statement; therefore the documents are not enclosed.

Office actions on the merits have been issued in related application numbers 10/829,674 (Examiner J. Goldberg; attorney docket 30847/2048-004) and 10/830,477 (Examiner S. Gembeh; attorney docket no. 30847/2051-005). The Examiners in those cases have raised patentability issues with respect to claims in those cases, and the Patent Office is encouraged to review the image file wrappers (IFW) in those cases for relevance to this application. The Applicants do not agree with any of the rejections and have filed responses to the actions in those cases, or are in the process of doing so.

III. Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

The Patent Office rejected claims 212 and 213 for alleged lack of written description of "pro-drugs". The Patent Office alleges that the specification does not provide a description of the structure of a representative number of species for the recited genus of "prodrugs of BAY-X-1005." The Applicants respectfully traverse.

The pro-drug recited in claim 212 would be metabolized into BAY-X-1005, and the structural formula provided for BAY-X-1005 provides adequate written description for pro-drugs to a person of ordinary skill in the art because of the similarity in structure that any pro-drug of BAY-X-1005 would necessarily have. In this way, the pro-drug situation is entirely distinct from the *Fujikawa* case cited by the Examiner, pertaining to whether a laundry list of substituents provides adequate description of a species. Instead, the genus is adequately defined both structurally (i.e., the structure of BAY-X-1005) and functionally (i.e., the activity of BAY-X-1005), requiring a conclusion that adequate written description exists.

A recent search of the PTO's issued patent database shows that the PTO has issued over 2400 patents since 1976 with "pro-drug" in the claims, which supports the Applicant's position that a drug provides adequate description for pro-drugs thereof.

Because pro-drug is adequately described, the rejection of claims 212-213 should be withdrawn.

IV. The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

The Patent Office rejected claims 206, 208, 209, 211-213 and 216-217 under 35 U.S.C. §103, alleging that the claimed invention was obvious in view of a combination of references. The applicants respectfully traverse.

A. The Isakson reference (and these cited tangentially in the PTO's discussion of Isakson) is irrelevant to the invention.

Isakson (US Patent No. 6,136,829), the primary reference cited by the Examiner, pertains to allegedly novel treatments for inflammation using a combination of COX-2 inhibitors and 5-lipoxygenase (5-LO) inhibitors. First, it is important to note that because the Isakson reference pertains to treatments requiring a COX-2 inhibitor, Isakson suggests nothing whatsoever about the claimed subject matter, which do not specify a COX-2 inhibitor. Second, Isakson's teachings concern BAY-X-1005 are conflicting at best. Isakson provides details and specific examples of the COX-2 inhibitors while providing a long laundry list of 5-LO inhibitors, which included BAY-X-1005, for use in the claimed combination therapies. It is important to note that BAY-X-1005 is a 5-LO Activating Protein (FLAP) inhibitor and indirectly inhibits 5-LO activity. Isakson defines "5-lipoxygenase inhibitor" as compounds which selectively inhibit 5-LO with an IC_{50} of less than about 10 μM (col. 9, lines 52-56) and it is unclear whether Isakson intended to include FLAP inhibitors in the definition of 5-LO inhibitors. For example, it is not clear that Isakson would assert that an inhibitor of protein that is different from 5-LO constituted a "selective" inhibitor of 5-LO.

Isakson provides experimental data relating to the effectiveness of the combination therapies using a COX-2 inhibitor in combination with the 5-LO inhibitors N'[3-[5-(4-Fluorophenenoxy)furyl-2-yl]-methyl-2-propylnyl]-N'-hydroxyurea and 6[[3-Fluoro-5-(3,4,5,6-tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy]methyl]-1-methyl-1H-quinolin-2-one. These specific 5-LO inhibitors are not BAY-X-1005. The Examiner stated that Isakson teaches administering BAY-X-1005 to patients suffering from myocardial inflammatory conditions. However, Isakson actually lists myocardial ischemia (also known as angina) as one of a long list of inflammatory conditions that may be treated with the combination therapies. Isakson does not particularly mention myocardial infarction (MI) and does not suggest that any of the contemplated therapeutic combinations would reduce CRP levels in a human at risk for MI. It is also worth noting that the class of drugs known as COX-2

inhibitors, which Isakson and Khanapure (discussed below) purport to disclose, has been the subject of high profile reports because they *increase the risk of heart attacks in patients* (American Heart Association (2005, November 14) ScienceDaily. Retrieved November 29, 2007, from http://www.sciencedaily.com/releases/2005/11/051114112914.htm; exhibit A).

The Examiner refers to Khanapure (published application 2002/0119977) when discussing the Isakson reference. Khanapure also pertains to allegedly novel COX-2 inhibitors. A FLAP inhibitor is mentioned only tangentially as one of many possible therapeutic agents to combine with the COX-2 inhibitor. *Even using impermissible hindsight, it is difficult to see how one of ordinary skill would find any relevance of Khanapure to the claimed invention.* The examiner cites paragraphs 0507 of Khanapure, which is one of many paragraphs containing laundry lists of agents that can purportedly be combined with Khanapure's alleged COX-2 inhibitors. There is no suggestion in Khanapure that BAY-X-1005 should be used alone or in combination with Khanapure's compounds for cardiovascular purposes, as opposed to other purposes in Khanapure that were unmentioned in the rejection. (See, e.g., paragraph 0505.) The reality is that Khanapure spends many pages listing hundreds of compounds that might be combined with Khanapure's alleged COX-2 inhibitors, and the notion that Khanapure "teaches" anything to a person of ordinary skill about leukotriene inhibitors in general, or BAY-X1005 in particular, is ludicrous. Khanapure, like Isakson, fails to teach or suggest anything about a therapeutic regime that does not include a COX-2 inhibitor as its principle ingredient.

The Examiner also refers to Datta *et al.* (*Biochem J.* 340: 371-375, 1999) in her discussion of the Isakson reference. Datta *et al.* demonstrates that the pro-apoptotic effects of MK886, a FLAP inhibitor, are mediated independently of FLAP. The apoptotic effects of known FLAP inhibitors are irrelevant to the invention, and it is unclear how Datta supports the notion that Isakson would indicate that the claimed invention is obvious to one of skill in the art.

The Examiner provides case law to support that if the prior art teaches a chemical structure that is identical to that claimed, the properties of that compound claimed are necessarily present in the prior art. The present claims are directed to methods of

reducing C-reactive protein (CRP) levels in human subjects at risk for MI by administering a FLAP inhibitor. Applicants are not disputing that the chemical structure of BAY-X-1005 was known in the art; however, the methods of administering BAY-X-1005 for reducing CRP was not suggested by the art and particularly not suggested by the references cited by the Examiner.

B. The invention is not obvious in view of Isakson in combination with Rossoni

Rossoni *et al.* teaches that pretreatment with BAY-X-1005 protected the rabbit ischemic heart from increased coronary perfusion pressure and injury related to an acute MI induced by coronary artery ligation. In the discussion below, the Applicants explain that Rossoni is irrelevant to the claimed invention. First, Rossoni describes an animal model that purports to model an infarction (coronary artery ligation) and then study what effects a drug has post-infarction. Thus, it is not even clear what Rossoni contributes to the knowledge about the benefit of the drug regime tested in the post-infarction model that was employed.

> Atherosclerotic lesions are asymmetrical focal thickenings of the innermost layer of the artery, the intima. It is commonly believed that inflammation plays a key role in all steps of atherogenesis, from its initial steps of endothelial dysfunction, through its development of mature atheroma and its serious complications, plaque rupture and thrombosis. The vulnerability of plaques to rupture depends on the amount of inflammatory cells within the plaque and the consistency of the atheromatous core; the soft plaques, *i.e.* rich in extracellular lipids, being more vulnerable. The most important clinical complication of atherosclerosis of the coronary arteries is the acute occlusion of the artery when a plaque ruptures, resulting in an infarction (damage) to the myocardial tissue (myocardial infarct = MI). Without intending to be limited to a particular theory, the present invention is based in part on the premise that a FLAP inhibitor, such as BAY-X-1005 (DG-031) will exert its anti-inflammatory effects (by reducing LTB4 production and CRP levels) on plaques, making the plaques less vulnerable to rupture. The Rossoni *et al.* reference cited by the PTO provides no insight or suggestion of the invention. Rossoni *et al.* used an experimental model in rabbits, in

which the anterior coronary artery was ligated with a suture, so as to close off the artery and induce acute myocardial infarction.

BAY-X-1005 was administered to the rabbits before and during the ligation. The effect of the trauma caused by the blockage of the artery was subsequently assessed by determining the mortality rate of animals up to 72 hours post-operation and measureing creatine phosphokinase activity, MPO activity and ECG. The ligation of the coronary artery resulted in acute infarction, as indicated by the high mortality rate of 60% after 72 hours (p. 338, Table 1), compared with sham-operated rabbits. Intravenous treatment of rabbits with BAY-X-1005 resulted in reduction of mortality rate, compared with ligation-operated rabbits (p. 388 Table 1). However, the authors do not give statistics for the difference in mortality rate between rabbits that underwent coronary artery ligation and received BAY-X-1005 treatment vs. those rabbits that underwent artery ligation without BAY-X-1005 treatment. It is not clear from the paper whether the drug had a statistically significant protective effect on the rabbits receiveing an artificially induced infarct.

It should also be noted that the rabbit model used by Rossoni *et al* does not at all mimic the biological events *leading up to* the formation of plaques, the development of inflammation, an increase in CRP levels or the ultimate rupture of the plaque. The model purports to model the ultimate post-injury result, *i.e.* what happens after the rupture of the plaque and blockage of the artery, but such a model is not useful for assessing the capability of a potential therapy to either reduce CRP levels, to prevent the formation of plaques, or prevent or delay the rupture of the plaques. Thus, the skilled person would not interpret the results presented by Rossoni *et al.* in such a way that they indicated that treatment with BAY-X-1005 could redcue CRP levels in a human subject at risk for MI. Succinctly put, a study of a drug's effect *while* (or after) surgically mimicking MI in rabbits provides no guidance whatsoever about the possible effects of the drug for reducing an inflammatory marker (CRP) in a human at risk for MI.

Furthermore, it is very unpredictable to extrapolate the effect of a drug in a human using a rabbit study that is not substantiated by experimental data obtained in human clinical studies. The study in Rossoni *et al.* was carried out on an otherwise healthy rabbit heart in which the coronary artery was ligated to induce an acute MI. The rabbits are herbivores that are not affected by the same genetic and environmental risk factors for cardiovascular disease as human subjects at risk for MI who would receive BAY-X-1005 to

reduce CRP levels using the claimed methods (Russell & Procter, *Cardiovas. Res.* 15: 318-330, 2006; Exhibit B). Furthermore, there are significant physiological and anatomical differences between the hearts of different species which make it unpredictable to determine how a drug will affect a human based on an animal study (Klocke *et al. Cardiovas. Res.* 74: 29-38, 2007). Rossoni *et al.* is one experiment carried out in a healthy rabbit heart and therefore would not render the claimed methods of administering BAY-X-1005 to reduce CRP in humans at risk for MI obvious (alone or in combination) with any of the references cited by the Examiner.

C. The Gompertz reference is irrelevant to MI or the invention.

The Gompertz reference also does nothing to negate patentability (alone or in combination with other references). Gompertz does demonstrate that BAY-X-1005 is effective in humans at reducing a measurable leukotriene, LTB4. However, Gompertz was a study that looked at patients with *chronic obstructive pulmonary disease (COPD)*, a term referring to two *lung diseases*, chronic bronchitis and emphysema, that are characterized by obstruction to airflow that interferes with normal breathing. The present invention, in contrast, is about reducing CRP levels in a human at risk for MI. It is also worth noting that, while much of the Patent Office's discussion of Gompertz focuses on monitoring blood, the Gompertz study actually took measurements from *sputum* (which the Examiner acknowledges but continues to discuss blood and plasma). The mention of measurements from blood at page 293 is in the context of discussing a different study by Fischer et al., cited in Gompertz.

D. No motivation to combine and no suggestion of the invention, even when combined.

The Patent Office alleges that one or ordinary skill would have been motivated to combine the cited references "to monitor the patient sera (plasma) level by first assaying for patients with high levels of leukotriene proteins, since the reference (Rossoni *et al.* Teach administering BAY-X-1005 lowers MI." To the contrary, Isakson did not use the BAY-X-1005 compound to treat anything but rather mentions using 5-LO inhibitors (rather than FLAP inhibitors, such as BAY-X-1005) in a combination with a COX-2 inhibitor, Gompertz

involved a pulmunary disease, and Rossoni involved rabbits. Furthermore, none of these references (alone or in combination) mention or suggest a reduction of CRP levels induced by inhibition of FLAP activity. Thus, the motivation to combine is entirely absent.

E. Bynum and FLAP genotypes.

Claim 225 involves "determining a FLAP genotype or haplotype of a human subject, and selecting for treatment a human subject with a FLAP genotype or haplotype that correlates with an increased risk of myocardial infarction." Bynum made a FLAP knockout mouse. The ability to knockout a gene in laboratory mice has nothing whatsoever to do with human genotyping. Bynum does not disclose or suggest determining a human FLAP genotype or haplotype at all; does not disclose or suggest that any human variation in FLAP genes exists; and does not disclose, suggest, or enable identifying a human FLAP genotype that correlates with an increased risk of MI. The existence and identification of such at-risk haplotypes is an invention of deCODE's and is the subject of this application and co-pending applications.

It also should be noted that the Patent Office offered no reason why one of ordinary skill would combine Bynum with any other reference cited by the Patent Office to reject other claims.

F. Conclusion with respect to obviousness.

The Patent Office has failed to cite any reference or reference combination that suggests that an inhibitor of FLAP activity in general, or BAY-X-1005 in particular, would be useful for reducing CRP levels in a human subject at risk for MI. The references cited by or referred to by the Examiner do not suggest that administration of BAY-X-1005 would reduce CRP levels in a human subject at risk for MI. None of the references mention reduction in CRP levels and do not teach one of skill in the art anything related to CRP levels. Isakson and Khanapure disclose therapies comprising COX-2 inhibitors, Datta *et al.* provides insight into the mechanism of FLAP inhibitor-induced apoptosis, Rossoni *et al.* investigates a rabbit model, Gompertz teaches therapies for pulmonary disorders and Bynum provides a FLAP gene knock out mouse. There is no link between these references and there is no reason for one of skill in the art to combine these references to carry out the claimed

invention. Therefore, the claims are not obvious in view of the cited references and Applicants request that the rejection under 35 U.S.C. § 103 be withdrawn.

VI. Double patenting rejections

The Applicants request that all provisional double patenting rejections be deferred until such time as there is an indication that subject matter is otherwise allowable in one of the pending applications. The applicants will cancel claims or file terminal disclaimers if necessary to obviate a double patenting rejection.

CONCLUSION

In view of the foregoing remarks, the Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the claims currently under examination, as well as linked claims that should be rejoined upon allowance of the generic claims.

Dated: November 30, 2007

Respectfully submitted,

By /Sharon M. Sintich/
Sharon M. Sintich
Registration No.: 48,484
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant